Therapy for Retinopathy of Prematurity

Information sheet

Dear Parents/Legal Guardian,

Your child

has been diagnosed with retinopathy of prematurity that needs to be treated. This information sheet supplements the explanation given to you by the treating doctor. It sets out in more detail how the treatment will proceed and why repeated visits to the ophthalmologist will still be essential even once treatment is completed.

Please take time to read carefully through this information sheet and use the blank lines on the last page to write down your questions. You can then ask all your questions during the consultation and discuss them with your doctor.

What is retinopathy of prematurity?

Retinopathy of prematurity is an eye disorder that is usually seen in very premature babies. It is seen most often in children who are born before 31 weeks of pregnancy. The name of the disorder, retinopathy of prematurity, is shortened to ROP. The abbreviation ROP is also commonly used in Germany.

The eyes of a newborn are usually only fully developed at the calculated due date of delivery. This is particularly relevant in the retina of the eye as the network of blood vessels is only complete at the calculated due date. The retina is a layer of tissue that lines the inside of the eye like a carpet. It is responsible for converting light signals received in the eye to electrical signals which are sent to the brain.

If a baby is born too early, the retina is often not completely lined with blood vessels. Areas of the retina without blood vessels can release various factors, including the growth factor VEGF (vascular endothelial growth factor), that can stimulate the blood vessels to grow into areas that do not have an adequate supply. However, very high concentrations of these growth factors can lead to uncontrolled growth of the vessels, including in some cases outside the retina towards the vitreous body. The vitreous body is a clear fluid inside the eye between the retina and the lens. The newly grown blood vessels can pull mechanically on the retina and detach it. Untreated detachment of the retina can lead to permanent loss of vision or even blindness.

The earlier the pregnancy ends and the smaller a baby is when born, the greater the area of the retina that does not have blood vessels. This is why babies born before the end of 31 weeks of pregnancy or who weigh less than 1500 g when born have a greater risk of vision loss or need treatment.

Course of retinopathy of prematurity (ROP) without treatment

Mild and early stages of ROP often improve without any treatment. However, if a certain stage is reached, the treatment should be started relatively soon, usually within a few days. In this situation, if treatment is not carried out or is carried out too late, subsequent measures may no longer be able to prevent irreversible damage or retinal detachment. Therefore, it is important to plan check-ups of your baby's eyes so that treatment can be started at the right time.

What options are there to treat retinopathy of prematurity (ROP)?

Certain advanced stages of ROP must be treated to prevent the retina detaching. This stage of the disorder is called 'threshold ROP' and must be treated. The two most common types of treatment are laser therapy and the injection of VEGF inhibitors.

The principle behind laser therapy is to stop overgrowth of new blood vessels by treating the areas without vessels around the edge of the retina. The individual laser focal points form scars on the retina, which reduces the oxygen needed in the tissue and the release of growth factors.

Another option to treat ROP is to inject active substances called VEGF inhibitors into the eye. These active substances block the overgrowth of new vessels by binding and inactivating the growth factors that trigger the growth. VEGF inhibitors are injected into the vitreous body through a needle. There are now different medications available that can be used for this injection therapy for ROP. You will find more information about the different medications below.

Both these treatment options (laser therapy and injection) mean that many babies with threshold ROP can be treated successfully, provided that the disorder is detected early. Cryotherapy (freezing a specific part of the eye) or surgical procedures are more rarely used.

Although the cause and the course of ROP is now very well known, and the disorder has been well studied, not all the details of the disorder are understood. In rare cases, despite treating the disorder in time and repeated check-ups, the retina may be damaged or become detached, leading to a loss of vision.

a) What happens with laser therapy

Laser therapy is usually carried out under general anaesthesia. You will be given a separate explanation of the general anaesthesia by an anaesthetist or neonatologist. For the laser therapy, the part of the retina where there are no blood vessels yet is destroyed (coagulated) by applying many laser spots. As a reminder, the part of the retina without blood vessels produces different factors that cause vessels to grow vigorously and can lead to the retina detaching. If this part of the retina is coagulated by the laser, the concentration of the growth factors can be lowered. The vessels in the retina are then no longer stimulated to (excessive) growth, which reduces the disease activity. The central part of the retina (the macula, where vision is the sharpest) that is essential for vision is not treated with the laser, which means it will still function properly after the disorder has improved. After the laser therapy, eye drops are often administered for several days. What is important are the check-ups to make sure the

laser treatment has worked.

b) Risks and possible side effects of laser therapy

- The laser therapy or photocoagulation is carried out with the greatest care. However, it is possible that despite the treatment there is a loss of vision or that additional measures or operations are needed as part of the treatment.
- Depending on the size of the area of retina without blood vessels in your baby's eye, that is, how big an area is coagulated with the laser during the procedure, the reduction in the field of vision or the night vision can vary.
- The laser treatment can in very rare cases cause clouding of the lens of the eye. Over time, the lens may need to be replaced in a surgical procedure.
- In rare cases, after laser treatment, a delicate membrane that resembles connective tissue forms on the surface of the retina. This membrane can pull together, which can lead to folds in the retina.
- There is a greater likelihood of severe shortsightedness after laser treatment than there is after injection treatment.
- Technical malfunctions of the instruments used (e.g. failure of the laser) are unlikely but cannot be completely ruled out and can cause inadequate treatment results, even in some cases causing the treatment to be stopped.
- If the laser therapy is effective, more procedures to treat the retina are usually not needed. **Your baby's eyes must still be regularly checked.**

Please ask your doctor about anything that is important to you or not yet clear.

c) What happens with the injection with an anti-VEGF medication

Depending on the general health of the baby, the anti-VEGF medication can be injected under general anaesthesia or local anaesthesia. The treating doctor will make the decision about this in a discussion with you and the other treating doctors. The eyes, the surrounding skin and the eyelids are carefully cleaned before the injection with a disinfectant to reduce the number of germs around the eyes. Using a sterile (germ-free) eyelid retractor, your baby's eyelids are held open during the procedure. Using a germ-free and very fine needle, the anti-VEGF medication is injected into the vitreous body. The process of injecting the medication only takes a few seconds. We know, from injecting adults who do not have a general anaesthetic, that the injection is usually painless but sometimes they experience a slight feeling of pressure.

After the injection, antibiotic eyedrops are usually administered for a few days to prevent inflammation or infection of the eye.

d) Risks and possible side effects of injection therapy

- Of course, the injection therapy is carried out with the greatest care. However, it is possible that despite the treatment there is a loss of vision or that additional measures or operations are needed as part of the treatment.
- In very rare cases, damage to the eye lens may occur during the injection therapy. Over time, the lens may need to be replaced in an operation.
- As a result of the injection into the vitreous body, in very rare cases germs may end up in the eye, and a bacterial infection may develop inside the eye (endophthalmitis). To detect such an infection as soon as possible, your baby's eyes will be examined a few days after the treatment so that any treatment with medications can be started immediately if there have been unwanted side effects. If there is a severe infection, an operation may be needed to drain it.
- After the injection, some of the active substance may leave the eye and enter your baby's body. The active substance can bind to the growth factor VEGF in your baby's body. Whether this affects the overall development of a premature baby has not yet been determined. There are follow-up observations available for this therapy since about 2006. The next section (f) explains the difference between the medications used.
- As a result of an injection into the eye, the pressure inside the eye can rise. In rare cases, medications that reduce the pressure have to be administered as eyedrops or into veins. An operation may also be needed in very rare cases.
- In very rare cases the injection may damage the retina leading to retinal detachment. This could require surgery.
- The disinfection of the skin and conjunctiva may in rare cases damage the skin or tissue. If disinfectants that contain iodine are used, thyroid overfunction or underfunction may develop.
- **The activity of the ROP may increase again, even a long time after the injection therapy. The eyes of a baby that have been treated with VEGF inhibitors must therefore be regularly checked every one to three weeks over a period of several months. This can be done as an outpatient. These check-ups are extremely important. If it cannot be guaranteed that you can attend these check-ups with your baby, the decision to have the injection therapy should be critically questioned and the alternative treatment of laser therapy, for example, should be considered.**

Please ask your doctor about anything that is important to you or not yet clear.

e) General treatment risks, including general anaesthesia risks, for all treatments

- As part of the general anaesthesia that is often needed to treat ROP, in very rare cases life-threatening complications may develop that need to be treated with additional measures.
- As with all medical procedures, during the treatment of ROP allergic reactions, including cardiovascular collapse or organ failure, may develop that need to be treated with additional measures.
- After both laser therapy and injection therapy, ROP usually improves within a few days or weeks. If it does not, this may possibly mean that the treatment did not work well enough, and a repeat treatment may be needed or a different treatment method should be used.
- Because threshold ROP occurs in both eyes in most cases, treating both eyes is often necessary. Risks and possible side effects of laser or injection therapy can therefore occur in both eyes. This is the case whether both eyes are treated on the same day or on separate days.
- It is possible that the activity of the disease decreases at first, but over time (typically after a few weeks or months) increases again. This is referred to as reactivation of ROP. A repeat treatment may then be necessary. A change of therapy may also make sense in this case. Additional check-ups of the retina are therefore essential.
- If the disease activity increases, and the retina starts to detach, an operation may be needed.
- Bleeding in the vitreous body may also occur. If the blood does not spontaneously clear up over time, it may need to be removed surgically.

f) Comparison of the different medications for injection therapy

Only the medication Lucentis® (active substance: ranibizumab) in a dose of 0.20 mg is currently approved in Germany to treat retinopathy of prematurity. However, there are other medications that are used to treat the disorder without approval, which is described as off-label use (see below for more information). Avastin® (active substance: bevacizumab) was the first medication in this class of active substances that was studied as part of a larger clinical trial of ROP. Another medication, Eylea® (active substance: aflibercept) was also studied as part of a clinical trial of the treatment of ROP. The decision for approval of Eylea® (aflibercept) for the treatment of ROP is still pending (as of March 2022).

Approval for a medication means that an independent authority has inspected the documents submitted by the manufacturing pharmaceutical company relating to this medication; after evaluating this information, the independent authority has issued an approval for a medication to treat a specific disease. If there is no approval, this means that the medication has not (yet) been reviewed by this independent authority. If such a medication is used nevertheless, this is called 'off-label' use. For ROP, this currently affects all anti-VEGF medications except for Lucentis® (ranibizumab), which has been approved for the treatment of ROP in Europe since 2019. If treatment is administered outside the approved indication (off-label use), there is no product liability for the pharmaceutical company. This does not mean, however, that the treatment takes place without liability. As usual, doctors are liable for the quality of treatment that they provide and pharmacists are liable for the quality of the ready-to-use medication that they prepare.

All the medications mentioned above for the injection treatment are injected directly into the eye in the same way. Over time, some of the active substance moves into the bloodstream where it can affect

the amount of the growth factor VEGF that is present. For the medication Lucentis® (ranibizumab), the medication is in the bloodstream for a very short time and is quickly excreted from the body. The studies showed that ranibizumab has no measurable effects on the VEGF level in the bloodstream. Avastin® (bevacizumab) and Eylea® (aflibercept) may stay longer in the bloodstream (up to several weeks), where these medications can measurably lower the VEGF concentration. Whether this affects other growth processes in the body of a premature baby is not yet clear.

Success, advantages, and drawbacks of laser therapy and injection therapy

Both treatment options are very likely to decrease the disease activity and preserve your baby's vision. However, there is no guarantee of success for either treatment options, laser therapy or injection therapy. It may be that repeat treatment is needed with both treatment options. The success rates in clinical trials with only one treatment are between 66% and 82% for laser therapy and between 80% and 86% for anti-VEGF therapy with Lucentis® (ranibizumab) or Eylea® (aflibercept).[1, 2] All other babies in these trials needed two or more treatments.

Repeat treatments for the injection therapy may also be needed later in the course of treatment. To make sure that disease activity does not increase again, your baby will need more check-ups over a much longer period after injection therapy than after laser therapy. On the other hand, after laser therapy is there is a greater likelihood of your baby having more severe shortsightedness.

The table below summarises some advantages and drawbacks of the two treatment options:

	Laser therapy	**Injection of VEGF inhibitors**
Advantages	• No treatment-related risk of an infection in the eye • Often only one treatment is needed • Check-ups after the treatment usually end earlier than after injection therapy • More long-term results available	• Procedure is relatively short, so brief general anaesthesia or local anaesthesia can be used • Severe shortsightedness occurs less often than after laser • Less loss of peripheral vision (retinal tissue is not destroyed) • Effect starts earlier, even in the first few days after treatment
Drawbacks	• Procedure lasts longer, so general anaesthesia usually needed • Loss of retinal tissue by coagulation (scars cause loss of peripheral vision) • Treatment effect takes longer to develop (several days) • Greater likelihood of severe shortsightedness than after injection therapy	• Increased but still very low risk of an eye infection that threatens visual function • Repeating the treatment is needed more often compared to laser therapy • More check-ups are needed for longer than after laser • Side effects in the rest of the body are plausible but have not yet been confirmed • Relatively new method so there is less long-term data

What happens after the treatment?

For both treatment alternatives, the baby must not rub the treated eye after the procedure. Because

the eye may still be anaesthetised, rubbing the eye may damage its surface. This can cause pain or inflammation. In some cases therefore, the eye will be covered with a bandage for several hours after the procedure. A few days after the treatment, the eye will be examined to confirm the success of the treatment and to check if any complications have developed.

For both treatment options, the retina must be examined at regular intervals by an ophthalmologist to check how the blood vessels are developing. In some cases, a repeat treatment of the retina may be needed. To ensure that the timing for a required repeat treatment is not missed, regular ophthalmological check-ups are carried out after administering a VEGF inhibitor, in some cases over a period of several months (including after discharge from the hospital). The check-ups can only be stopped when the blood vessels cover the entire retina or if no negative changes are seen over a period of several months after the injection.

It is very important that ophthalmological check-ups are not missed without consulting the treating doctor.

It is best if you mark in red in your calender the appointments needed for the check-ups after a treatment. There is also a **ROP passport**, which can be added to your baby's health record. The check-up appointments can be recorded in the passport. Ask your doctor for more information. The ROP passport can help to make sure that no appointments are missed.

If you cannot attend an ophthalmological check-up, immediately contact your ophthalmologist and make an alternative appointment as close to the original as possible.

You can write down any questions that you would like to discuss with the doctor on the blank lines below.

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References:

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Editorial notes:

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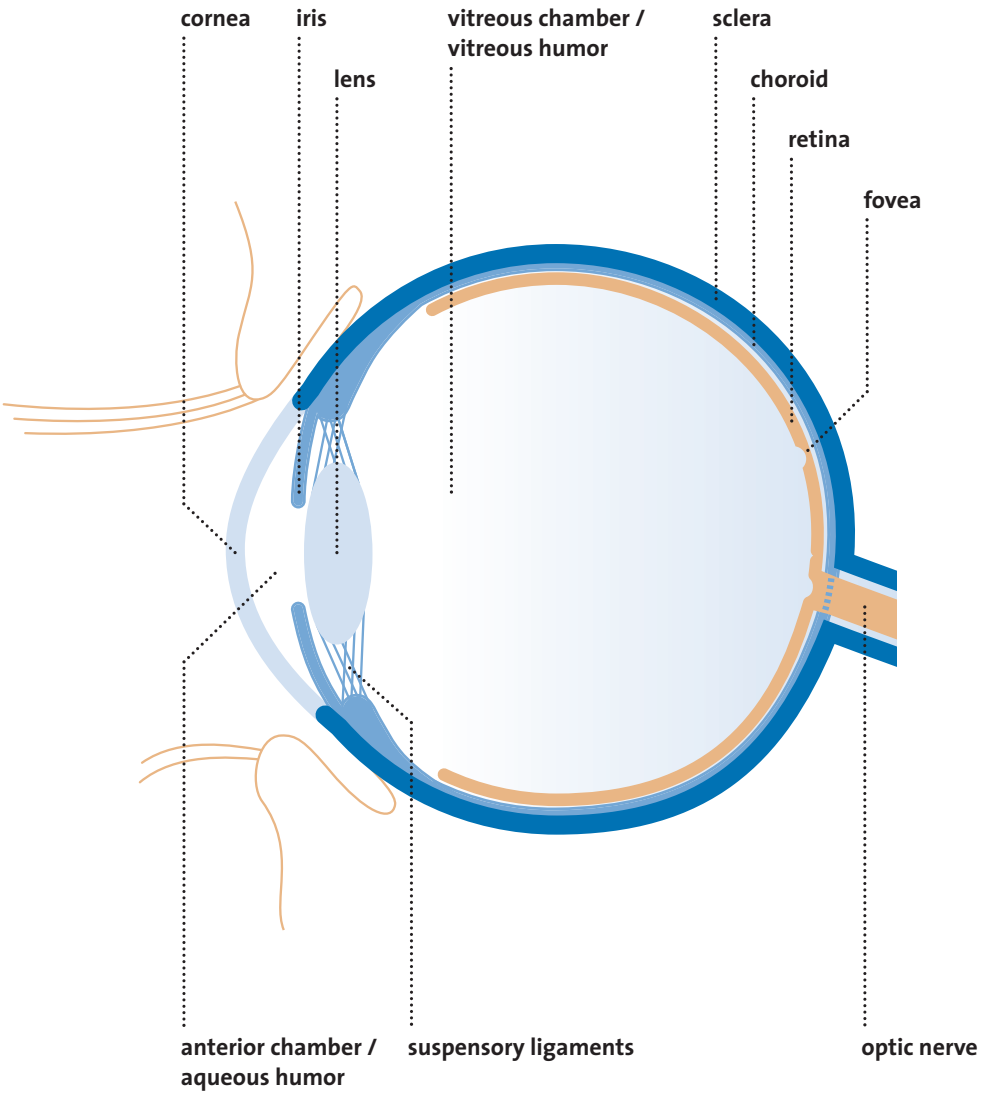
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